

L Number	Hits	Search Text	DB	Time stamp
1	1	cfr same peptide same open same probability	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/14 14:23
2	27	cfr same peptide same activator	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/14 14:23
3	0	adams-lynn-m.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/14 14:24
5	2	ma-jianjie.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/14 14:25
4	8	davis-pamela-b.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/01/14 14:25

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=> file medline biosis embase caplus
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=> s cftr (p) activat? (p) peptide (p) open (p) probab?
L1      8 CFTR (P) ACTIVAT? (P) PEPTIDE (P) OPEN (P) PROBAB?
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=> d 12 total ibib kwic

AB The cystic fibrosis transmembrane conductance regulator (**CFTR**) is a cAMP-dependent protein kinase- and ATP-regulated chloride channel, the activity of which determines the rate of electrolyte and fluid transport in a variety of epithelial tissues. Here we describe a mechanism that regulates **CFTR** channel activity, which is mediated by PDZ domains, a family of conserved protein-interaction modules. The Na(+)/H(+) exchanger regulatory factor (NHERF) binds to the cytoplasmic tail of **CFTR** through either of its two PDZ (PDZ1 and PDZ2) domains. A recombinant fragment of NHERF (PDZ1-2) containing the two PDZ domains increases the **open probability** $P(o)$ of single **CFTR** channels in excised membrane patches from a lung submucosal gland cell line. Both PDZ domains are required for this functional effect, because **peptides** containing mutations in either domain are unable to increase channel $P(o)$. The concentration dependence of the regulation by the bivalent PDZ1-2 domain is biphasic, i.e., **activating** at lower concentrations and inhibiting at higher concentrations. Furthermore, either PDZ domain alone or together

is without effect on P(o), but either domain can competitively inhibit the PDZ1-2-mediated stimulation of **CFTR**. Our results support a molecular model in which bivalent NHERF PDZ domains regulate channel gating by crosslinking the C-terminal tails in a single dimeric **CFTR** channel, and the magnitude of this regulation is coupled to the stoichiometry of these interactions.

L2 ANSWER 2 OF 2 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2000131261 MEDLINE
DOCUMENT NUMBER: 20131261 PubMed ID: 10666038
TITLE: PKA holoenzyme is functionally coupled to CFTR by AKAPs.
AUTHOR: Huang P; Trotter K; Boucher R C; Milgram S L; Stutts M J
CORPORATE SOURCE: Departments of Medicine and CF/Pulmonary Research and Treatment Center, University of North Carolina, Chapel Hill, North Carolina 27599, USA.. Pingbo_Huang@med.unc.edu
CONTRACT NUMBER: HL-42384 (NHLBI)
HL-533094 (NHLBI)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. CELL PHYSIOLOGY, (2000 Feb) 278 (2) C417-22.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000427
Last Updated on STN: 20000427
Entered Medline: 20000414

AB Cystic fibrosis transmembrane regulator (**CFTR**) is reported to be preferentially regulated by membrane-bound protein kinase A (PKAII). We tested for close physical and functional association of PKA with **CFTR** in inside-out membrane patches excised from Calu-3 cells. In the presence of MgATP, 8-(4-chlorophenylthio)adenosine 3',5'-cyclic monophosphate (CPT-cAMP) increased the product of **CFTR** channel number and **open probability** (from 0.36 +/- 0.12 to 1.23 +/- 0.57, n = 20, P < 0.0025), and this stimulation was abolished by PKI. Thus Calu-3 membrane isolated from cells retains PKA holoenzyme that is functionally coupled to **CFTR**. PKAII is anchored at specific subcellular sites by A kinase anchoring proteins (AKAPs). Exposure of excised patches to HT-31, a **peptide** that disrupts the association of PKAII and AKAPs, prevented CPT-cAMP stimulation of **CFTR**. Therefore, PKA holoenzyme in isolated membrane patches is bound to AKAPs. In whole cell voltage-clamp studies, intracellular dialysis of Calu-3 cells with HT-31 blocked the **activation** of **CFTR** by extracellular adenosine. These results suggest that AKAPs mediate PKA compartmentalization with **CFTR** and are required for **activation** of **CFTR** by physiological regulators.

=> s adams lynn /au
L3 5 ADAMS LYNN

=> s davis pamela /au
L4 17 DAVIS PAMELA

=> s ma jianjie /au
L5 146 MA JIANJIE

=> d his

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FILE 'MEDLINE, BIOSIS, EMBASE, CAPLUS' ENTERED AT 14:31:41 ON 14 JAN 2004
L1 8 S CFTR (P) ACTIVAT? (P) PEPTIDE (P) OPEN (P) PROBAB?

L2 2 DUP REM L1 (6 DUPLICATES REMOVED)
L3 5 S ADAMS LYNN /AU
L4 17 S DAVIS PAMELA /AU
L5 146 S MA JIANJIE /AU

=> s cftr (p) activat? (p) peptide
L6 212 CFTR (P) ACTIVAT? (P) PEPTIDE

=> s cftr (p) activator (p) peptide
L7 23 CFTR (P) ACTIVATOR (P) PEPTIDE

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8 7 DUP REM L7 (16 DUPLICATES REMOVED)

=> d l8 total ibib kwic

L8 ANSWER 1 OF 7 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:419394 BIOSIS
DOCUMENT NUMBER: PREV200200419394
TITLE: Function and specifics of a biological resource including
pancreatic cell lines.
AUTHOR(S): Hay, Robert J. [Reprint author]
CORPORATE SOURCE: American Type Culture Collection, Manassas, VA, USA
SOURCE: Proceedings of the American Association for Cancer Research
Annual Meeting, (March, 2002) Vol. 43, pp. 1049. print.
Meeting Info.: 93rd Annual Meeting of the American
Association for Cancer Research. San Francisco, California,
USA. April 06-10, 2002.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Aug 2002
Last Updated on STN: 7 Aug 2002

IT
& Systems of Organisms
beta cell: endocrine system; liver: digestive system; stomach:
digestive system

IT Chemicals & Biochemicals
ARIP: biomarker; **CFTR**: expression; CSF-1; activin A;
azaserine: expression; betacellulin; dexamethasone; gastric mucin:
secretion; glucagon-like **peptide**-1 [GLP-1]; glucose; insulin:
secretion, synthesis; islet duodenal homeobox-1 [IDX-1]: beta-cell
differentiation factor; plasminogen **activator**

L8 ANSWER 2 OF 7 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2001434728 MEDLINE
DOCUMENT NUMBER: 21212873 PubMed ID: 11316265
TITLE: Differences in the protein-kinase-A-dependent regulation of
CFTR Cl⁻ channels and Na⁺-K⁺ pumps in guinea-pig
ventricular myocytes.
AUTHOR: Kockskamper J; Sendhoff K; Erlenkamp S; Bordusa F; Cerovsky
V; Glitsch H G
CORPORATE SOURCE: Loyola University Chicago, Stritch School of Medicine,
Department of Physiology, Maywood, IL 60153, USA..
jkocksk@luc.edu
SOURCE: PFLUGERS ARCHIV. EUROPEAN JOURNAL OF PHYSIOLOGY, (2001 Mar)
441 (6) 807-15.
Journal code: 0154720. ISSN: 0031-6768.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB Protein-kinase-A- (PKA-) dependent regulation of cystic fibrosis transmembrane conductance regulator (CFTR) Cl- current (I(CFTR)) and Na+-K+ pump current (Ip) was studied in single guinea-pig ventricular myocytes. Both currents were measured simultaneously by means of whole-cell recording at 30 degrees C. The adenylyl cyclase activator forskolin was used to stimulate PKA activity. At -20 mV, forskolin (4 microM) induced a fast activation of I(CFTR) and a delayed stimulation of Ip. Despite the strikingly different time courses, however, the potency of the drug to regulate both currents was identical. Half-maximal activation of I(CFTR) and stimulation of Ip, respectively, were observed at 9.6×10^{-8} M and 9.9×10^{-8} M forskolin. Inclusion of a specific peptide inhibitor of PKA in the pipette solution (PKI, 20 microM) blocked forskolin's effect on Ip. However, regardless of the time allowed for cell dialysis, there still was a marked, transient activation of I(CFTR), which could be prevented by: (1) a short pre-activation of I(CFTR) with forskolin or (2) the additional inclusion in the pipette solution of a synthetic peptide (Ht31 peptide, 60 microM) that interferes with PKA binding to its anchoring proteins. Thus, there is a tight functional coupling between PKA and CFTR Cl- channels in guinea-pig ventricular myocytes. The coupling is probably due to the close physical proximity of channels and kinases. . . .

L8 ANSWER 3 OF 7 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2002018354 MEDLINE
DOCUMENT NUMBER: 21338101 PubMed ID: 11444148
TITLE: Guanylin in the human pancreas: a novel luminocrine regulatory pathway of electrolyte secretion via cGMP and CFTR in the ductal system.
AUTHOR: Kulaksiz H; Schmid A; Honscheid M; Eissele R; Klempnauer J; Cetin Y
CORPORATE SOURCE: Department of Molecular Cell Biology, Institute of Anatomy and Cell Biology, Philipps University, Robert-Koch-Strasse 6, 35033 Marburg, Germany.
SOURCE: HISTOCHEMISTRY AND CELL BIOLOGY, (2001 Feb) 115 (2) 131-45. Journal code: 9506663. ISSN: 0948-6143.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20020121
Last Updated on STN: 20020121
Entered Medline: 20011204

AB Cystic fibrosis transmembrane conductance regulator (CFTR) is a channel and regulator protein that is crucially involved in transepithelial ion transport. In the exocrine pancreas, the CFTR-mediated secretion of an electrolyte-rich fluid is a major but as yet incompletely understood function. We show here that the peptide guanylin is a specific activator of CFTR function in the human pancreas implicating regulation of pancreatic electrolyte secretion. Guanylin and its affiliated signaling and effector proteins including guanylate cyclase C, cGMP-dependent protein kinase II, CFTR, and the epithelial Cl-/HCO3- exchanger, anion exchanger 2, are highly expressed in the human pancreas. Guanylin is localized specifically to. . . pathway of electrolyte secretion in the ductal system. Functional studies in two different human pancreatic duct cell lines expressing the CFTR Cl- channel that is functionally intact in CAPAN-1 cells but defective (delta F508) in CFPAC-1 cells clearly identify guanylin as a specific regulator of pancreatic

CFTR channel function. Whole-cell patch-clamp recordings in CAPAN-1 cells revealed that forskolin induces an increase of Cl⁻ conductance mediated by cAMP. . . . we conclude that guanylin is an intrinsic pancreatic regulator of Cl⁻ current activation in pancreatic duct cells via cGMP and **CFTR**. Remarkably, in the pancreas guanylin may exert its function through an intriguing luminocrine mode via the pancreatic juice.

L8 ANSWER 4 OF 7 MEDLINE on STN DUPLICATE 3
 ACCESSION NUMBER: 1999137573 MEDLINE
 DOCUMENT NUMBER: 99137573 PubMed ID: 9950772
 TITLE: Cloning, characterization, and functional expression of a CNP receptor regulating CFTR in the shark rectal gland.
 AUTHOR: Aller S G; Lombardo I D; Bhanot S; Forrest J N Jr
 CORPORATE SOURCE: Department of Medicine, Yale University School of Medicine, New Haven, Connecticut 06510; and Mount Desert Island Biological Laboratory, Salisbury Cove, Maine 04672, USA.
 CONTRACT NUMBER: DK-34208 (NIDDK)
 P30-ES-3828 (NIEHS)
 SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY, (1999 Feb) 276 (2 Pt 1) C442-9.
 Journal code: 0370511. ISSN: 0002-9513.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 OTHER SOURCE: GENBANK-AF054285
 ENTRY MONTH: 199903
 ENTRY DATE: Entered STN: 19990413
 Last Updated on STN: 19990413
 Entered Medline: 19990330

AB In the shark, C-type natriuretic **peptide** (CNP) is the only cardiac natriuretic hormone identified and is a potent **activator** of Cl⁻ secretion in the rectal gland, an epithelial organ of this species that contains cystic fibrosis transmembrane conductance regulator (**CFTR**) Cl⁻ channels. We have cloned an ancestral CNP receptor (NPR-B) from the shark rectal gland that has an overall amino. . . . but lacks a glycosylation site and a Glu residue previously considered important for CNP binding. When shark NPR-B and human **CFTR** were coexpressed in *Xenopus* oocytes, CNP increased the cGMP content of oocytes (EC50 12 nM) and activated **CFTR** Cl⁻ channels (EC50 8 nM). Oocyte cGMP increased 36-fold (from 0.11 +/- 0.03 to 4.03 +/- 0.45 pmol/oocyte) and Cl⁻. . . . +/- 14 to -1,226 +/- 151 nA) in the presence of 50 nM CNP. These findings identify the specific natriuretic **peptide** receptor responsible for Cl⁻ secretion in the shark rectal gland and provide the first evidence for activation of **CFTR** Cl⁻ channels by a cloned NPR-B receptor.

L8 ANSWER 5 OF 7 MEDLINE on STN DUPLICATE 4
 ACCESSION NUMBER: 97246495 MEDLINE
 DOCUMENT NUMBER: 97246495 PubMed ID: 9115758
 TITLE: C-type natriuretic peptide increases chloride permeability in normal and cystic fibrosis airway cells.
 AUTHOR: Kelley T J; Al-Nakkash L; Drumm M L
 CORPORATE SOURCE: Department of Pediatrics, Willard Bernbaum Cystic Fibrosis Center, Case Western Reserve University, Cleveland, Ohio 44106-4948, USA.
 CONTRACT NUMBER: HL-50160 (NHLBI)
 P30 DK27651 (NIDDK)
 T32 HL07451 (NHLBI)
 SOURCE: AMERICAN JOURNAL OF RESPIRATORY CELL AND MOLECULAR BIOLOGY, (1997 Apr) 16 (4) 464-70.
 Journal code: 8917225. ISSN: 1044-1549.
 PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 19970506
Last Updated on STN: 20000303
Entered Medline: 19970423

AB C-type natriuretic **peptide** (CNP), a hormone which stimulates particulate guanylate cyclase activity, was studied for its ability to stimulate chloride permeability through the cystic fibrosis transmembrane conductance regulator (**CFTR**) in airway epithelial cells. Two cell lines, Calu-3 and CF-T43, were used as models of normal and cystic fibrosis (CF) airway epithelial cells, respectively. Calu-3 cells, derived from a lung carcinoma, express relatively high levels of wild-type **CFTR**. CF-T43 is a transformed line derived from a nasal polyp and expresses the mutant **CFTR**, deltaF508. Calu-3 cells exposed to the nucleotide guanosine-3',5'-monophosphate (cGMP) analogue 8-Br-cGMP exhibit increased ³⁶Cl⁻ efflux, demonstrating that cGMP can mediate. . . . Calu-3 monolayers. Whole-cell currents stimulated by CNP display linear current-voltage relationships and have inhibitor pharmacology and ion selectivity consistent with **CFTR** channel activity. Sodium nitroprusside (SNP), an **activator** of soluble guanylate cyclase, and CNP both increase cGMP levels and short circuit current in Calu-3 cells. In contrast, exposure. . . isoproterenol and SNP showed no increase in chloride efflux. Together, these data indicate that CNP can activate wild-type and mutant **CFTR** through a cAMP-dependent protein kinase pathway and that the sensitivity of Calu-3 cells for this stimulation is greater than that. . . .

L8 ANSWER 6 OF 7 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 96064750 MEDLINE
DOCUMENT NUMBER: 96064750 PubMed ID: 7592887
TITLE: Isotype-specific activation of cystic fibrosis transmembrane conductance regulator-chloride channels by cGMP-dependent protein kinase II.
AUTHOR: French P J; Bijman J; Edixhoven M; Vaandrager A B; Scholte B J; Lohmann S M; Nairn A C; de Jonge H R
CORPORATE SOURCE: Department of Cell Biology, Faculty of Medicine and Health Sciences, Erasmus University, Rotterdam, The Netherlands.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Nov 3) 270 (44) 26626-31.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951221

AB . . . alpha cGK (cGKI) purified from bovine lung were compared for their ability to activate the cystic fibrosis transmembrane conductance regulator (**CFTR**)-Cl⁻ channel in excised, inside-out membrane patches from NIH-3T3 fibroblasts and from a rat intestinal cell line (IEC-CF7) stably expressing recombinant **CFTR**. In both cell models, in the presence of cGMP and ATP, cGKII was found to mimic the effect of the catalytic subunit of cAMP-dependent protein kinase (CAK) on opening **CFTR**-Cl⁻ channels, albeit with different kinetics (2-3-min lag time, reduced rate of activation). By contrast, cGKI or a monomeric cGKI catalytic fragment was incapable of opening **CFTR**-Cl⁻ channels and also failed to potentiate cGKII activation of the channels. The CAK activation but not the cGKII activation was blocked by a CAK inhibitor **peptide**. The slow activation by cGKII could not be ascribed to counteracting protein phosphatases, since neither calyculin

A, a potent inhibitor. . . by cGKII closed instantaneously upon removal of ATP and kinase but reopened in the presence of ATP alone. Paradoxically, immunoprecipitated **CFTR** or CF-2, a cloned R domain fragment of **CFTR** (amino acids 645-835) could be phosphorylated to a similar extent with only minor kinetic differences by both isoforms of cGK. Phosphopeptide maps of CF-2 and **CFTR**, however, revealed very subtle differences in site-specificity between the cGK isoforms. These results indicate that cGKII, in contrast to cGKI alpha, is a potential **activator** of chloride transport in **CFTR**-expressing cell types.

L8 ANSWER 7 OF 7 MEDLINE on STN DUPLICATE 6
 ACCESSION NUMBER: 92042003 MEDLINE
 DOCUMENT NUMBER: 92042003 PubMed ID: 1718974
 TITLE: Functional insertion of the SV40 large T oncogene in cystic fibrosis intestinal epithelium. Characterization of CFI-3 cells.
 AUTHOR: Chastre E; Di Gioia Y; Barbry P; Simon-Bouy B; Mornet E; Fanen P; Champigny G; Emami S; Gespach C
 CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale U.55, Unite de Recherches sur les Peptides Neurodigestifs et le Diabete, Paris, France.
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1991 Nov 5) 266 (31) 21239-46.
 Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199112
 ENTRY DATE: Entered STN: 19920124
 Last Updated on STN: 19960129
 Entered Medline: 19911213

AB . . . the human cytoke-
 ratin 18 gene and poorly differentiated by phase-contrast and electron microscopy. Functional membrane receptors activated by vasoactive intestinal **peptide** (VIP), its natural analogue pituitary adenylyl cyclase activating **peptide** (PACAP-38), and isoproterenol were observed in CFI-3 cells. Restriction fragment length polymorphism analysis of the PstI KM19 site revealed that the **cftr** locus was identical in the chorionic villi and in CFI-3 cells. The manifestation of CF in this family was not. . . by the 125I efflux, was induced in CFI-3 cells by the calcium ionophore ionomycin, but not by the adenylyl cyclase **activator** forskolin, and was inhibited by the chloride channel blocker 5-nitro-2-(3-phenylpropylamino)benzoic acid. These results were confirmed in patch clamp studies in. . . phenotype relating to defective regulation of Cl- channels, and therefore constitute a suitable model, 1) for elucidating the function of **CFTR** protein, 2) developing new therapeutic agents, and 3) correcting the CF defect by gene replacement therapy in vitro.